Acute pyogenic meningitis

Objectives:

- Define acute pyogenic meningitis.
- Recall the epidemiology of acute pyogenic meningitis.
- Recall the etiologic agents according to the age and common serotypes of the main causative pathogens.
- Describe the clinical presentation of acute meningitis.
- Identify microbiology of common causative agents including the morphology.
- Identification, pathogenesis and complications of meningitis
- Discuss approaches to the clinical diagnosis of acute meningitis case with emphasis on lab diagnosis and comparison between normal and abnormal CSF analysis.
- Recall the management of acute meningitis with emphasis on rapid diagnosis and selection of empirical antimicrobial therapy for the common pathogens.
- Recall preventative strategies (vaccination and prophylaxis) used against common pathogens.



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MICTOBIOLOGY



Acute Pyogenic Meningitis

Pyogenic Meningitis⁽¹⁾

A serious infection that causes inflammation of the meninges^[2] affecting the pia, arachnoid and subarachnoid space, and it is associated with marked inflammatory exudation



Characteristics

- Acute onset
- Usually caused by bacterial infections
- \circ May be preceded by URTI ^[3]
- Can be **fatal** if left untreated

Common etiologic agents

- Neisseria meningitidis
- Streptococcus pneumoniae
- Haemophilus influenzae

★ Causes according to the age			
Age	Pathogens		
Newborns	Group B Streptococcus (strept.agalactiae), E. coli (and other gram negative bacilli) Listeria monocytogenes.		
Infants / Children	S. pneumoniae, N. meningitidis, H. influenzae.		
Adults	S. pneumoniae, N. meningitidis, Listeria Monocytogenes also if the patient >50y		
Special circumstances ^[4]	<u>S. aureus</u> , S. epidermidis, S. pneumoniae , anaerobes, P. aeruginosa.		

^[1] Pyogenic because there are pus cells

⁽⁴⁾ Dr:Not the focus of our lecture, and it's mainly happen after neurosurgical procedures and skull fractures

⁽²⁾ Membranous coverings of the brain consists of 3 layers dura mater, arachnoid Mater and pia mater

⁽³⁾ Bacterial meningitis is a rare but potentially fatal disease. It can be caused by several types of bacteria that first cause an upper respiratory tract infection then it will go to the left side of the heart and then travel through the bloodstream to the brain

Epidemiology of Meningitis

- A worldwide disease, about 1.2 million cases annually and 135,000 deaths.
- $\circ~$ Bacterial meningitis is one of the top ten infections that causes death worldwide.
- Half of the survivors suffer neurological damage, and/or permanent side effects afterwards.

Signs & Symptoms of Acute Meningitis					
Most common (children and adults)	FeverSevere HeadacheStiff neck.	 Nausea & vomiting Sensitivity to light Confusion 			
In infant ⁽¹⁾ (Neonates and young children)	InactivityIrritability	VomitingPoor feeding			
Advanced cases	• Bruises under skin (rapidly spread). ^[2]				
Advanced disease	Brain damageComaDeath				
Physically demonstrable symptoms of meningitis	Brudzinski's sign	Severe neck stiffness (due to the inflammation of the meninges) causes the patient's hips and knees to flex when the neck is flexed.			
	Kernig's sign	Severe stiffness of the hamstrings cause an inability to straighten leg when the hip is flexed to 90 degrees.			

 $^{(l)}$ all these symptoms in infants are not-specific but if you see the infant with it you will suspect meningitis.

⁽²⁾ As the infection progresses, blood vessels can become damaged, usually happen with S.pneumoniae and N.meningitidis

★ You MUST know the morphology & lab findings as it will come as hints in the exam

		1- Listeria Monocytogenes	A 0 0 0	Small Rods (basilli) Aerobes Tumbling motility Facultative intracellular	A	Extra
ecture (Extra 438) Gram Positive	n Positive	2- S. Pneumonia	A 0 B 0 C 0 0	Diplococci Alpha-hemolytic Optochin sensitive Catalase -ve Coagulase -ve	A C C C	B C
	Gran	3- Group B Streptococcus (streptococcus agalactiae)	A 0 B 0 0 0	Cocci in chains Beta hemolytic Catalase -ve Coagulase -ve Bacitracin Resistant	A	B
s in This L	s in This L	4- E. Coli	A	Rods Lactose fermenter Oxidase -ve	Α	B
Pathogen Gram Negativ	Gram Negativ	5- Neisseria Meningitidis	A 0 B 0 C 0 D 0 0 0	Kidney bean shaped diplococci Latex particle agglutination Utilises maltose and glucose Grows on thayer-martin agar Catalase and Oxidase +ve Grows on chocolate agar		B D
		6- H.Influenzae	А 0 В 0	Requires growth factor: X (Hemin) and V (NAD) Coccobacilli	A	В

1- Listeria Monocytogenes				
Morphology	 Gram +ve rods (diphtheroids like) Human intestinal colonization (2-12%) 			
Risk Factors	• Causes meningitis in newborns and immunosuppressed patients and elderly.			
Pathogenesis	 Widespread among animals in nature including those associated with certain foods (cheese and meat) Spread to fetus following hematogenous spread in mother or from birth canal. Has tropism^[1] to the CNS 			

⁽¹⁾ Tissue tropism is the cells and tissues of a host that supports growth of a particular virus or bacterium. Some bacteria and viruses have a broad tissue tropism and can infect many types of cells and tissues

Etiologic Agents

2- S. Pneumoniae			
Morphology	• Gram +ve diplococci		
Risk Factors	 Skull Trauma Unvaccinated patients (infection rate decreased with vaccination) 		
Pathogenesis	 S. Pneumococcal meningitis may follow Pneumococcal Pneumonia or other infections caused by this bacteria^[1] Capsule is a polysaccharide polymer Pneumolysin^[2] toxin decreases inflammatory immune response and leads to severe infection. 		
Prognosis	 Recovered cases develop sustained (long period) learning disabilities High mortality rate >30% due to invasive disease 		

3- Group B Streptococcus agalactiae (GBS)			
Morphology	 Gram +ve cocci in chains Resident bacteria in GIT & vagina (10-30%)^[3] 		
Risk Factors	 Premature rupture of membrane Prematurity^[4] Low infant innate immunity 		
Pathogenesis	 Gain access to amniotic fluid during delivery or colonize newborn during passage through birth canal^[5] Causes sepsis and meningitis in the first few days of life and after 4 weeks 		

4- E. Coli			
Morphology	 Gram -ve bacilli Most common cause of neonatal meningitis Many features similar to GBS (Group B Streptococcus) 		
Pathogenesis	 Vaginal E.coli colonize infant via rupture of amniotic membrane or during birth. Failure of preterm maternal IgM to cross placenta & special susceptibility of newborn. K1 sialic acid capsule of some strains invade brain microvascular endothelial cells. 		

⁽¹⁾Remember, meningitis was a feared complication of otitis media.
 ⁽²⁾ A pore-forming toxin
 ⁽³⁾ Colonizes the mother's git & vagaina, and transmits to the newborn during delivery
 ⁽⁴⁾ born before the end of the full term of pregnancy
 ⁽⁵⁾ We do screening for the mother in week 24. If she was colonized with this bacteria and a risk of premature rupture was suspected, prophylaxis must be given.

Etiologic Agents

	5- N. Meningitidis (referred to as meningococcus)
Morphology	 Gram -ve diplococci oxidase-positive present in the nasopharynx of 10% of people (potentially pathogenic)
Transmission	• Inhalation of aerosolized droplets & close contact ^[1]
Prevalence ^[2]	• Common in children who are younger than 6 and young adults
Risk Factors	• Susceptible individuals Unvaccinated people ^[3]
Serotypes	 B,C,Y,W135 cause isolated ,sporadic small epidemics in close population. ★ Serotype A has an epidemic potential in Sub-Saharan Africa (meningitis belt)^[3]
Pathogenesis	 Colonization of nasopharynx → Septicemia → crosses blood brain barrier endothelial damage → activation of coagulation cascade → thrombosis and platelets aggregation → bleeding : skin rash and adrenal hemorrhage Shortly: Colonization of nasopharynx → Septicemia → crosses blood brain barrier → Meningitis It stimulates antibody production in carriers Pili attach to microvilli of nasopharynx → invasion → bacteremia endotoxin LPS (lipopolysaccharide) produced which spreads to the meninges Capsule resists phagocytosis
Prognosis	 11-20% of recovered patients suffer permanent hearing loss, mental retardation while 10-14 % of cases are fatal

6- H.Influenzae (B)				
Morphology	 Small gram -ve coccobacilli Has polysaccharide capsule, other H. Influenza species has no capsule. Need blood for optimal growth, Hematin (factor X) and NAD (factor V) Found in the nasopharynx normal flora Major cause of lower RTI; occasionally invade deeper tissues and cause bacteremia. Bacteremia : bacteria spread to the CNS ,bones or other organs 			
Serotypes	 Many serotypes a-f H.influenzae <u>Type B</u> has a capsule made of a polymer of PRP (Polyribosylribitol Phosphate) that causes acute life threatening invasive infections 			
Prognosis	 3-6% mortality rate 1/3 of survivals have significant neurological sequelae Infection rate decreased since the routine use of Hib vaccine 			

^[1] Kissing, coughing, sneezing, sharing drinks or a cigarette, etc

⁽²⁾Also it's common in college age students especially in Europe because of the close living and sharing equipment. adults usually infected by S.pneumoniae but in this case N.meningitidis is more common

⁽³⁾ Given the way it transmits and its epidemiology, in 2000, there was a meningococcal outbreak in the kingdom during hajj season which involved people from 16 different countries. A year after the incident, meningococcal vaccination became a mandatory visa requirement for all pilgrims from any country; no meningococcal outbreak was reported in Saudi Arabia during the 2002 Hajj season
 ⁽⁴⁾ The African meningitis belt is a region in sub-Saharan Africa where the rate of incidence of meningitis is very high. The primary cause of meningitis of the belt is Neisseria

Diagnosis of Meningitis

- • Clinically: Sign & symptoms
- **Specimens:** CSF analysis acquired through lumbar Diagnosis of puncture and blood specimen for Meningitis culture.
- CSF is analyzed for cells, proteins, glucose and chloride in addition to culture and antimicrobial susceptibility testing.

Dr: No need to remember specific numbers, just know if it's increased or decreased (Normal range will be provided)

CNS PARAMETERS					
	Normal CS	F	Pyogenic Meningitis		
Adults	 WBC =0-5 /cmm3 PMN^[1]= 0 % glucose = > 60 % of blo protein =< 30 mg/dl chloride = 115-130mmol 	od /l	 ↑WBC= 5 - 5000/cmm3 ↑PMN^[1]= > 60% 		
Neonates	Term (mature): WBC =0-32 /cmm3 PMN=>60 % glucose = >60 % of blood protein= 20-170 mg/dl	Preterm (premature): WBC=0-29/cmm3 PMN= <60 % glucose = >60 % of blood protein= 60-150 mg/dl	 ↓Glucose⁽²⁾ = < 45 % of blood ↑Protein⁽³⁾ = >60 mg/dl ↓Chloride = 110 mmol/l 		

CSF Evaluation					
Condition WBC		Protein (mg/dL)	Glucose (mg/dL)		
Normal	<5, ≥75% lymphos	20-45	>50 (or 75% serum glucose)		
Bacterial, acute	100-10,000 or more; usually 300-2,000; <mark>Neutrophils</mark> predominate	Usually 100-500	Decreased, usually <40 (or <50% serum glucose)		
Bacterial, partially treated	5-10,000	Usually 100-500	Low to normal		
ТВ	10-500 Lymph	100-3000	<50		
Viral or meningoencephalitis	Rarely > 1000 Lymph	Usually 50-200	Generally normal; may Viral or be decreased		

⁽¹⁾Polymorphonuclear leukocytes

⁽²⁾ It decreases because of the inflammation and increased consumption of glucose.

⁽³⁾ "increases because there is a lot of inflammation and cell destruction.

Abnormal findings of CSF in some pathological conditions					
Parameter	Bacterial Meningitis	Tuberculous Meningitis	Viral Meningitis	Brain Tumor	
Protein	↑ ↑	↑ ↑	Normal	Ť	
Glucose	ţţ	ţţ	Normal or slightly \downarrow	Ļ	
Chlorides	ĻĻ	↓↓	Normal or \downarrow	Normal or \downarrow	

Management

- A medical emergency.
- Antibiotics given after taking specimens for lab diagnosis^[1].
- Parenteral administration.^[2]

Children & Adults	 Ceftriaxone^[3] (or Cefotaxime) + Vancomycin^[4] (covers the main 3 pathogens). Add ampicillin if the patient age is > 50 or at risk for Listeria.
Neonates ⁽⁵⁾	 ★ Ampicillin + Gentamicin + Cefota<u>xime^[6]</u> ○ Modify treatment after lab results (as needed)
Duration	\circ 10-14 days (or more) according to the medical condition
Prevention	 Vaccination Prophylactic antimicrobial agent for contacts (Hib^[7] & N. meningitidis)

^[1] empirical treatment

 $^{\mbox{[2]}}$ Non-oral route for administration such as I.V

⁽³⁾ Ceftriaxone / Cefotaxime to cover Neisseria and Haemophilus

^[4] Vancomycin to cover Gram positives. Both can cover Pneumococcus

(6) 3 antibiotics to cover E.coli, Group B and listeria
 (6) Not Ceftriaxone because it's contraindicated for neonates <28 days
 (7) H.Influenzae B

Drs' notes

Dr. Khalifa

- In cases of newborns and young infants (<1 year), it is difficult to see the classic signs of meningitis (neck stiffness and headache).
 Instead, they come with non specific signs such as fever, decreased movement, poor feeding, and irritability.
 - Neck stiffness can be felt when flexing the patient's neck. Flexing becomes difficult & painful.
 - N. Meningitidis is common in college students especially those with European & North American lifestyle. (they are in close proximity and share stuff such as drinks and cigarettes).
 - N. Meningitidis has many serotypes. Vaccines for types A, C, T, W135 were discovered a long time ago while effective vaccination for type B was discovered recently. Vaccine development was quite difficult due to structural differences and immunogenic differences.
 - To differentiate between Neisseria types, we use sugar utilization/fermentation test (bacteria is placed in glucose, maltose, and sucrose mediums then we see how it is reacts). N.Meningitidis is the only type that utilizes glucose and Maltose (other types cannot utilize maltose).
 - ★ In haij season, everyone gets vaccinated because we fear the epidemic of N. Meningitidis type A which is highly prevalent in African countries of meningitis belt.
 - N. Meningitidis can grow on blood agar and chocolate agar, but it cannot grow on McCouncy agar.
 - S.pneumoniae can cause meningitis on its own (in cases of skull trauma/fractures), or <u>through bacteremia after upper/lower</u> respiratory tract infections and sinusitis. S.pneumoniae is more virulent than N.meningitidis and it has a much higher mortality rates. Its main virulence factor is its capsule, pneumolysin, and autolysin.
 - H.influenzae can only grow on chocolate agar as it needs x & v factors, and it never grows on blood and McCouncy agars.
 H.influenzae used to be the main cause of severe invasive diseases, but nowadays, there is a decrease in its significance due to the development of an effective vaccine against type B (the most virulent type).
 - Routine screening is done for pregnant women and vaginal swab is taken. If colonization with group B strept is found, they will be given prophylaxis (ampicillin) to decrease the risk of transmission to the newborn.
 - Listeria is associated with certain foods such as cheese and cold meat because it can grow in decreased temperature (refrigerator). For most people, it causes self-limited mild gastroenteritis; however, it causes bacteremia and severe diseases in elderly and immunosuppressed. Pregnant women are recommended to avoid certain foods to decrease the risk of listeria transmission to the newborn. The pregnant women herself will only have mild gastroenteritis, however; it is feared that she will pass it to the fetus hematogenously or during delivery and cause meningitis to the baby.
 - ★ In the treatment of acute meningitis, we start with empiric treatment as it is considered to be a medical emergency. (1) In children and adults, we give ceftriaxone and vancomycin. Ampicillin is added if the patient is old >50. (2) In neonates, we give ampicillin, cefotaxime (because ceftriaxone is contraindicated for neonates), and gentamicin for additional coverage.

Prof. Hanan

Both N. Meningitidis and Neisseria species are residues of the nasopharynx. They differ in that N. Meningitidis is a pathogen while Neisseria sp is a normal flora (do not mix the two). Also, 10% of people are carriers of N. Meningitidis, but being a carrier of N. Meningitidis does not necessarily indicate meningitis.
 Differentiation between N. Meningitidis and other Neisseria is done by sugar fermentation test (N. Meningitidis ferments glucose & maltose, but never sucrose). More confirmation is done by latex agglutination test (a laboratory method used to detect certain antibodies or antigens).
 S.pneumoniae and S.viridans are both alpha hemolytic. Differentiation between the two organisms is done by positive optochin sensitivity test of S.pneumoniae, Gram stain, and latex agglutination test.
 H.influenzae is mainly diagnosed by its growth requirement (X&V factors). PolyribosylRibitol Phosphate (PRP) is a capsular polysaccharide and it contributes to the enhanced virulence of type B Haemophilus influenzae. Also, we do not see H.influenzae in neonates because they usually acquire immunity against it from the mother (immunity decreases by the time they are >5 years old).
 Bacitracin test is used to differentiate between group A & group B streptococci (GAS is sensitive/GBS is resistant).
 In addition to obtaining a CSF sample for the diagnosis of acute meningitis, taking a blood culture is VERY important as well (because there is septicemia in most of the cases, and because isolation of the bacteria from the CSF is not always successful).

Click on the icon to check out the team's summary			
Q1: Which of the following organisms has a capsule made of a polymer of PRP? A- S.Pneumonia B- E.Coli C- N.meningitidis D- H.Influenzae B Q2: Which one of the following is a virulence factor in meningitis causing-streptococcus pneumoniae	Q4: 23 days of age Khalid brought by his mom to the ER with irritability, vomiting, and poor feeding. The mother denied any prenatal screening tests. What's the most likely etiology? A- S. pneumoniae B- Group B strept. C- N. meningitidis D- S.aureus Q5: In relation to the previous question, what would be the empirical therapy?		
A- Pneumolysin B- Type I Pili C- P pili D- All of the above	A- Cefotaxime + Ampicillin + Gentamicin B- Cefotaxime + Vancomycin C- Ceftriaxone + Vancomycin D- Ceftriaxone + Ampicillin + Gentamicin		
Q3: Mansour, a 63 year-old male arrived to the ER with fever and neck stiffness. History revealed that he usually eats cold cuts. What's most likely causative organism? A- S.Pneumonia B- Group B Strept. C- N.Meningitidis D- Listeria monocytogenes	Q6: In comparison with normal CSF findings, which one of the following demonstrates abnormal CSF findings due to Bacterial Meningitis A- Increased WBC (mainly lymphocytes), increased protein, increased glucose, decreased chlorides B- Increased WBC (mainly lymphocytes), increased protein, decreased glucose, decreased chlorides C- Increased WBC (mainly neutrophils), increased protein, increased glucose, decreased chlorides D- Increased WBC (mainly neutrophils), increased protein, decreased glucose, decreased chlorides		

Quiz 🔲

SAQ

CASE: A college-age student came to the emergency department with his partner with two days history of high fever and severe headache. Examination revealed neck stiffness and positive Brudzinski's sign. the patient's partner is living with him and they both smoke cigarettes. Lumbar puncture was done to obtain CSF and gram's stain showed gram negative diplococci

Answers: Q1:D | Q2:A | Q3:D | Q4:B | Q5:A | Q6:D

Q1: What is the most likely diagnosis?

Acute Pyogenic Meningitis

Q2: What is the most likely causative agent?

N.meningitidis

Q3: How would you confirm the causative organism?

Maltose and glucose utilization test

Q4: A) How can this agent be transmitted? B) mention the susceptible individuals?

A: Close contact. B: Unvaccinated people

Q5: Briefly explain the pathogenesis

Q6: A) What is the appropriate treatment for this patient B) Duration of treatment?

A: Vancomycin + Ceftriaxone B: 10-14 days typically

Q7: What is the stereotype of this organism that has a pandemic potential?

Type A (highly prevalent in african countries of meningitis belt)

SAQ

CASE: One week old neonate was born via vaginal delivery. His mother noticed poor feeding, irritability, and decreased movement. CSF analysis showed high WBCs count mainly neutrophils, low glucose and high protein. -Dr.Khalifa

Q1: What is the most likely diagnosis?

Acute Pyogenic Meningitis

Q2: Enumerate the possible causative organisms?

Group B strept, Listeria, and E.coli

Q3: Empiric therapy indicated in this case?

Cefotaxime + Gentamicin + Ampicillin

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CASE: A 60-year-old man presented to the Emergency Department complaining of fever, neck pain, and severe headache. At the time of presentation, the level of consciousness was decreased (Glasgow Coma Score of 7) and he had apparent neck stiffness accompanied by Kernig's and Brudzinski's sign on physical examination. The patient was febrile at the time of examination (oral temperature of 39°C) and other vital signs were as follows: systolic blood pressure of 160 mmHg, diastolic blood pressure of 90 mmHg, heart rate of 110 beats per minute, and respiratory rate of 16 per minute. He had a recent history of a lower respiratory tract infection. CSF analysis showed a elevated white blood cell count, elevated proteins, and decreased sugar levels. Microbiology report came positive for Gram positive diplococci

Q1: What is the most likely diagnosis?

Acute Pyogenic Meningitis

Q2: What is the most likely causative agent?

Streptococcus pneumoniae

Q3: Briefly explain the pathogenesis of this case?

Lower respiratory tract infection \rightarrow bacteremia \rightarrow meningitis

Q4: What risk factors does this organism possess?

Capsule to resist phagocytosis and Pneumolysin

Q5: A) What is the appropriate treatment for this patient B) Duration of treatment?

A: Vancomycin + Ceftriaxone + Ampicillin (because the patient is >50 years old) B: 10-14 days typically

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CASE: A previously healthy 8 years old boy was admitted to the emergency department with a reduced level of consciousness after a day of flu-like symptoms, headache and vomiting. After arrival to the hospital, he appeared somnolent with a Glasgow Coma Score (GCS) of 9. Physical examination revealed nuchal rigidity with no focal neurological deficits. At admission, biochemical analyses revealed a neutrophil leucocytosis, elevated C reactive protein and procalcitonin levels, and arterial blood gas analysis showed a slight metabolic acidosis. Lumbar puncture revealed a cloudy cerebrospinal fluid (CSF) with elevated white blood cell count and protein levels, and a decreased CSF-serum glucose ratio. A contrast-enhanced CT scan of the brain was negative for signs of bleeding, oedema or hydrocephalus. Lab reported that the bacteria isolated from both CSF and blood cultures was a type B small Gram negative coccobacilli.

Q1: What is the most likely diagnosis?

Acute Pyogenic Meningitis

Q2: What is the most likely causative agent?

H.Influenzae (HiB)

Q3: What risk factors does this organism possess?

PRP (PolyribosylRibitol Phosphate) in its capsule

Q4: A) What is the appropriate treatment for this patient B) Duration of treatment?

A: Vancomycin + Ceftriaxone B: 10-14 days typically

Members Board

Team Leaders



Muneerah Alsadhan

Team Members

- Abdulaziz Alderaywsh
- Abdulrahman Alswat
- Albandari Alanazi
- **Faisal Alotaibi**
- Ibraheem Altamimi
- Leen Almadhyani
- Mayasem Alhazmi



Meshal Alhamed



Meshal Althunian

Note takers :

Duaa Alhumoudi •

Organizers :

Leena Almazyad

Reviser:

Noura Alshathri



- **Mohammed Beyari**
- **Mona Alomiriny**
- Noura Aldahash
- **Raed Alnutaifi**
- **Rand Alrefaei**
- Sadeem Alhazmi
- Sara Alharbi
- Tarfa Alsharidi
- Yara Alasmari
- **Faisal Alomri**



Sarah Alquwayz

